PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* 16 AUG 2005
see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220 29330

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2005/000481	05.05.2004	05.05.2004

International Patent Classification (IPC) or both national classification and IPC
C07D277/24, C07D277/34, C07D277/40, C07D417/04, C07D277/50, C07D417/12, C07D277/46, A61K31/426,

Applicant
RENOPHARM LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2005/000481

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1 -8, 9(part)-19(part), 20-26, 27(part)-198(part)

because:

☒ the said international application, or the said claims Nos. 62-74, 140-198 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☒ the claims, or said claims Nos. 1 -8, 9(part)-19(part), 20-26, 27(part)-198(part) are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	9-19, 27-198
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	9-19, 27-198
Industrial applicability (IA)	Yes:	Claims	9-19,27-61,75-139
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1- Present claims relate to an extremely large number of possible compounds and compositions. Support within the meaning of Art. 6 PCT and disclosure within the meaning of Art. 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope in impossible. Consequently, the search has been carried out for those parts of the claims which appears to be supported and disclosed, namely those parts relating to the compounds of claim 9 wherein B and Z are alkyl groups and Y is a NO releasing group as defined on page 40 (lines 24-33).

The preliminary examination will concern only the parts of the claims which have been searched (Rule 66.1 (e) PCT).

2-Claims 62-74 and 140-198 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims, cf. Article 34(4)(a)(i) PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1- Reference is made to the following documents:

d1: WO 01/49275 A (QUEEN'S UNIVERSITY AT KINGSTON; THATCHER, GREGORY, R., J; BENNETT, BRI) 12 July 2001 (2001-07-12)

d2: WO 03/086282 A (NITROMED, INC; FANG, XINQIN; GARVEY, DAVID, S; GASTON, RICKY, D; LIN,) 23 October 2003 (2003-10-23)

d3: KUMAR S ET AL: "Design, Synthesis, and Evaluation of alpha-Ketoheterocycles as Class C Beta-Lactamase Inhibitors" BIOORGANIC &

MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 9, 2001, pages 2035-2044, XP002206636 ISSN: 0968-0896

2- Novelty
Thiazole derivatives bearing a NO-releasing group are disclosed in d1 (cf. compounds IIIf of page 25, IVk of page 33, Vr of page 38 and Vy of page 39).
These compounds are excluded from the scope of present claims either because they have been disclaimed or because the group linking the NO-releasing moiety is not an alkylene chain (present group B).
Hence, the requirements of Art. 33.2 are met.

3- Inventive step
3.1- The applicant seems to have set himself the task of providing novel NO-donors which can be useful in the treatment of various conditions such as cardiovascular diseases, inflammation and tumor.
Documents d1 and d2 relate to compounds having the same use of present compounds.
Considering the chemical structures of the compounds disclosed in these documents, it is considered that d1 represents the closest state of the art.
For the purpose of assessing the inventive activity during the international stage, it is accepted that present compounds possess the claimed activity, i.e. that they are NO-donors.
Hence, the technical problem can be seen in the provision of further NO-donors.

3.2- The compounds disclosed in d1 are structurally very similar to the compounds of the invention. Compounds IIIf and IVk are excluded from the scope of the claims merely by means of a disclaimer.
From d1 the skilled person would deduce that thiazole derivatives, eventually substituted in position 4 by an alkyl group and bearing in position 5 a NO-releasing moiety attached to the ring through an alkylene chain, are suitable compounds as NO-donors.
The use of NO-releasing agents for the treatment of cardiovascular disorders is suggested by d2.
Hence, the provision of present compounds as NO-releasing agents does not involve any inventive skill.
The processes of claims 75-139 are based upon standard procedures as it can be

deduced from the reaction scheme 7 of d3.
Hence, also the process claims do not involve any inventive activity.